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Docetaxel-induced skin toxicities in breast cancer patients subsequent to paclitaxel shortage: a case series and literature review

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Abstract

Purpose—As the result of a recent national shortage in paclitaxel, some patients who were receiving or scheduled to receive weekly paclitaxel were converted to every 3-week (q3w) docetaxel with granulocyte colony-stimulating factor support. Our institution noted higher than expected incidence of severe skin toxicity events attributable to docetaxel during the shortage period among our breast cancer patients. In this report, we summarize the clinical course of the first five cases, review the literature surrounding docetaxel-induced skin toxicity, and offer possible prevention and treatment strategies to improve docetaxel tolerability.

Methods—The observation period for this case series was August 1 through October 21, 2011. All patients treated with docetaxel were identified from our electronic medical record. Operable stage I–III breast cancer patients who received 1 dose of docetaxel monotherapy at 75–100 mg/m² q3w were included in this study. The cases of grade 3–4 docetaxel-induced skin toxicities identified by the treating oncologists were then contacted and signed an informed consent through an Institutional Review Board-approved protocol.

Results—Thirty-four patients met the inclusion criteria. Five patients (14.7 %) experienced grade 3 skin toxicity events attributable to docetaxel, a significantly higher rate than previously reported for docetaxel dosed at 75–100 mg/m².

Conclusions—Docetaxel-induced dermatologic toxicity is well characterized; nonetheless, its etiology is largely unknown and evidence-based prevention and management strategies are lacking. This report shows that the use of docetaxel 75–100 mg/m² q3w subsequent to dose-dense doxorubicin and cyclophosphamide regimen can lead to unacceptable rate of severe skin toxicity.

Keywords

Taxane; Hand–foot syndrome; Breast cancer; Chemotherapy toxicity

Introduction

Doxorubicin and cyclophosphamide (AC) followed by a taxane is a commonly prescribed chemotherapy regimen for HER2/neu(–), high-risk invasive operable breast cancer [1]. Every 3-week dosing of AC (doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m²) was considered the conventional regimen until the pivotal Cancer and Leukemia Group B-9741 trial [2] report, which showed significant improvement in disease-free survival and overall survival in the dose-dense arm. Since the finding, the dose-dense regimen (every 2-week AC, same doses as every 3 weekly schedule) with granulocyte colony-stimulating factor (GCSF) support has become a chemotherapy cornerstone for the treatment of non-metastatic breast cancer. AC or dose-dense AC (ddAC) followed by weekly or dose-dense paclitaxel (TaxolTM) are two commonly prescribed adjuvant regimens for HER2/neu(–) breast cancer [1]. Paclitaxel is the preferred taxane because of comparable efficacy and better toxicity profile compared with docetaxel [3]. In response to the shortage of paclitaxel, our institution encouraged physicians to consider alternatives to paclitaxel whenever possible. Starting in August 2011, operable breast cancer patients who were receiving or scheduled to receive weekly paclitaxel (wP) 80 mg/m² after ddAC were converted to docetaxel (WinthropTM of Sanofi-AventisTM, Bridgewater, NJ) with GCSF support, based on similar efficacy from the phase III trial [3]. We have noted higher than expected incidence of severe skin toxicity events (defined as grade 3) attributable to docetaxel during the shortage period among our breast cancer patients, and therefore a case series study was instigated.

Patients and methods

This single institution case series has been approved by the Institutional Review Board at Ohio State University. The cases of grade 3–4 docetaxel-induced skin toxicities were identified by the treating oncologists and documented in the patient's medical record. A report was generated from the patient electronic record database (IHIS™) to identify patients based on the following inclusion criteria: (1) patients with operable stage I–III breast cancer treated at The Stefanie Spielman Comprehensive Breast Center from August 1 through October 21, 2011 and (2) 1 dose of docetaxel monotherapy at 75–100 mg/m² 3-weekly (q3w). Patients treated with trastuzumab/docetaxel combination therapy were excluded as trastuzumab-induced skin reactions could skew results. The grading of overall skin toxicities (skin and subcutaneous tissues disorder, other, specify) and hand–foot syndrome (palmar–plantar erythrodysesthesia syndrome) were based on Common Terminology Criteria for Adverse Events v.4.03. All subjects who met the above criteria were used as the denominator to calculate the incidence of severe docetaxel-induced skin toxicity in our study. The identified patients signed the informed consent prior to chart review, data analysis, and manuscript submission. No formal statistical analysis was performed due to the descriptive nature of this study.

Results

During the observation period, 34 patients were initiated on q3w docetaxel at 75–100 mg/m². We observed 14.7 % incidence of grade 3 skin toxicities, which was significantly higher than precedent observations in numerous randomized breast cancer trials with q3w docetaxel with routine corticosteroid premedication. Reported rate in prospective clinical trials utilizing adjuvant docetaxel in breast cancer population is approximately 3–5 % [3–8]. All five patients developed grade 3 skin toxicity and grade 3 hand–foot syndrome (HFS). The average onset of presentations was 3 days after docetaxel infusion. All but one affected patients received 100 mg/m² docetaxel q3w and all were premedicated with appropriate corticosteroid, antihistamine (50 mg IV diphenhydramine), and histamine-2 (H₂) receptor blocker (20 mg PO famotidine). We reviewed the cases' medication list and found no known drug–drug interactions that could have confounded our HFS rate, except for the proceeding use of ddAC chemotherapy. Below, we present the aforementioned five cases that occurred at our institution, followed by a review of literature surrounding the etiology and management of docetaxel-induced dermatologic toxicity.

Case 1

A 61-year-old postmenopausal woman was diagnosed with estrogen receptor positive, progesterone receptor positive, and Her2/neu negative, T1cN1M0 mucinous carcinoma of the left breast and ductal carcinoma in situ of the right breast. Past medical history (PMH) included hepatitis C without cirrhosis, laryngopharyngeal reflux, dysphonia, seasonal allergies, leukoplakia, asthma, and sinus drainage. She had received four cycles of adjuvant ddAC complicated by grade 2 diarrhea and mucositis which were adequately controlled with antidiarrheal medications and oral ice chips, respectively.

Subsequently, the patient received 100 mg/m² (body surface area, BSA=1.9 m²) of docetaxel on day 1 of cycle 1 followed by pegfilgrastim injection on day 2. Three days after her docetaxel infusion, she complained of a burning sensation on her hands. She was instructed to use a topical emollient cream and oxycodone or tramadol for pain. Unfortunately, her symptoms worsened, with significant swelling and erythema on her hands which impaired her ability to perform daily tasks. She went to the emergency department on day 5 and was subsequently hospitalized. On admission, she was found to have rash, numbness, and tingling of her feet and hands. The rash extended to her forearms

as depicted in Fig. 1. The rash was painful without itching and resulted in blistering. Periorbital edema was also noted. Her severe rash and HFS were both rated as grade 3. The patient denied any shortness of breath or throat swelling. She was started with empiric IV vancomycin and hydromorphone for pain control. Dermatology consult recommended cholesterolized petrolatum for scaling, aluminum acetate soaks to prevent infection, and application of cold compresses as needed. She was treated with oral dexamethasone and pyridoxine, with minimal effect on her symptoms. The patient was discharged home after 5 days and continued on a 14-day course of cephalexin and oral hydromorphone.

Four weeks after her initial docetaxel dose, her skin toxicities improved to grade 1. Her adjuvant chemotherapy was changed to wP at 80 mg/m² for nine doses. She completed seven wP infusions without skin toxicity, but treatment was stopped after seven doses secondary to taxane-induced grade 3 peripheral neuropathy.

Case 2

A 51-year-old previously healthy postmenopausal woman was diagnosed with T3N0M0, triple-negative infiltrating ductal carcinoma. Four cycles of ddAC was administered in the adjuvant setting complicated by grade 3 mucositis, which was treated with CaphosolTM (calcium chloride/sodium phosphate solution). She received her first docetaxel infusion (100 mg/m², BSA=1.76 m²) on day 1 and pegfilgrastim injection on day 2.

Two days after the docetaxel infusion, she experienced redness and swelling on her hands and feet. The patient was prescribed amoxicillin/clavulanate, hydrocodone/acetaminophen, and ibuprofen 800 mg. A grade 2 mucositis was observed and she was prescribed CaphosolTM and lidocaine/diphenhydramine/antacid oral suspension ("Magic Mouthwash," MMW). The following week, the patient presented with grade 3 HFS with ulcerative dermatitis and severe pain interfering with daily function. She was instructed to finish the entire course of amoxicillin/clavulanate, continue the pain medications, and apply aggressive skin emollient. Unfortunately, her HFS did not resolve and remained a grade 3 a week later. She also developed grade 3 neuropathy and was started on gabapentin. Her chemotherapy was deferred for 2 weeks, until her HFS and neuropathy improved to grade 1. Docetaxel was discontinued and wP at 80 mg/m² was started. She received seven of the nine prescribed paclitaxel infusions without skin toxicity, after which the treatment was terminated due to grade 3 neuropathy.

Case 3

A 56-year-old postmenopausal woman was diagnosed with T2N0M0, triple-negative, invasive ductal carcinoma. Significant PMH included diabetes mellitus, hypertension, and hyperlipidemia. After her left mastectomy, she had completed four cycles of ddAC with pegfilgrastim and tolerated AC relatively well, except for cycle 1, which was complicated by non-neutropenic fever of 38.3 °C. Patient was hospitalized for 1 day, resulting in a negative workup for infectious disease and resumed the full dose of AC chemotherapy. She was then started on her first of four planned cycles of docetaxel at 100 mg/m² (BSA=1.89 m²) and was given pegfilgrastim injection on day 2. Two days after her docetaxel dose, she developed pain over her hands and feet that was not relieved by acetaminophen or ibuprofen. The patient had difficulty walking and utilizing her hands due to the pain. She started on oral dexamethasone, hydrocodone–acetaminophen, and moisturizing cream. She experienced significant arthralgia and had limited ability to use her hands for 1 week. When the patient returned to clinic for cycle 2, the skin of her palms and soles had visible desquamation, but HFS had improved to grade 2. Given her history of grade 3 HFS, her docetaxel dose was reduced to 75 mg/m² q3w without GCSF support. She had completed the remaining cycles of reduced-dose docetaxel uneventfully.

Case 4

A 54-year-old premenopausal woman was diagnosed with T2N2M0 ER(+), PR(+), HER2/neu(-), grade 2, invasive ductal carcinoma. PMH included fibrocystic breast disease, infectious mononucleosis, arthritis, osteoporosis, hypothyroidism, detached vitreous humor, and vehicular trauma. She had finished four cycles of neoadjuvant ddAC with pegfilgrastim support, which was well tolerated except for mild arthralgia and mucositis. Her docetaxel dose was 100 mg/m² (BSA=1.9 m²), followed by pegfilgrastim injection on day 2.

Three days post-chemotherapy, the patient developed a fever of 38.1 °C accompanied by nonproductive cough and urinary frequency. Her urinalysis showed 2+ bacteria but was otherwise unremarkable. A complete blood count, chemistry panel, and blood and urine cultures were drawn. Chest X-ray was also obtained, which was unremarkable. She was treated with levofloxacin empirically. At that time, grade 1 HFS was noted, with redness on fingers without pain. She continued to experience intermittent low-grade fever for the next several days despite negative infection workup. Subsequently, her fingertips and soles of her feet became red and swollen with significant pain, skin peeling, and blistering (grade 3) along with numbness in her fingers and knees. Other toxicities included significant weakness; lightheadedness; fatigue; pain in the nail beds, jaw, and back; blurry vision with tearing and burning eyes; and nasal discharge. Docetaxel was switched to weekly albumin-bound paclitaxel (Abraxane™) at 125 mg/m² for nine doses. She received three doses of the agent without skin toxicity but it was subsequently held due to neutropenia and cytomegalovirus viremia.

Case 5

A 62-year-old postmenopausal woman was diagnosed with clinical stage III, triple-negative, high-grade invasive ductal carcinoma. PMH included chronic obstructive pulmonary disease, asthma, hypertension, hypercholesterolemia, migraines, peptic ulcer disease, and fibrocystic breasts. She was initiated on neoadjuvant chemotherapy with four cycles of ddAC followed by a taxane. She had finished and tolerated the ddAC well, except that cycle 4 was deferred for 1 week due to asthma exacerbation. Subsequently, she received docetaxel at 75 mg/m² (BSA=1.82 m²), followed by pegfilgrastim on day 3.

On day 4 following cycle 1 of docetaxel, she noted pruritus and tingling in her fingers and toes. She was instructed to take diphenhydramine every 6 h as needed. Unfortunately, over the course of the next 3 days, she developed prominent bilateral hand and finger swelling and erythema with mild scaling, accompanied by severe pervasive pain, and progressively worsening generalized pruritic rash. Other toxicities were grade 2–3 mucositis, nausea, and vomiting. The patient was hospitalized for severe pain. She was seen by a dermatologist in the hospital and started on oral pyridoxine, topical triamcinolone, and adequate skin moisturizer for grade 3 HFS. During her 5-day hospitalization, she was treated with morphine for pain, antiemetics for nausea and vomiting, and MMW for mucositis. When she returned to clinic for cycle 2, her HFS had improved from grade 3 to grade 2. Her chemotherapy regimen was switched to wP at 80 mg/m². She only received seven doses of wP due to grade 3 neuropathy.

Discussion

The incidence of grade >2 skin toxicities we observed (14.7 %) was significantly higher than precedent studies for docetaxel dosed at 75–100 mg/m². For example, in a landmark phase III trial by Eastern Cooperative Oncology Group (ECOG 1199), patients with operable, node-positive breast cancer who completed four cycles of adjuvant AC on q3w schedule were randomized to paclitaxel or docetaxel, each given either weekly or q3w. In this trial,

the incidence of grade 3 skin toxicities (including dry skin, erythema, HFS, pigmentation, pruritus, rash/desquamation, urticaria, dermatitis, and other) was <5.5 %. Hand–foot reaction, erythema, and desquamation occurred in 3–4 % of patients who received docetaxel q3w; compared to <2 and <0.5 % in the AC wP arm, respectively [3]. Comparatively, grade 3 skin toxicity and HFS were not identified as significant non-hematological adverse effects in the NSABP B-30 trial in both sequential and concurrent docetaxel arms [8].

The incidence of docetaxel-induced skin toxicity varies significantly across published studies, depending on the dose intensity, dosing frequency, premedication regimen, and cumulative dose. The reported incidence of all grades skin toxicity (excluding nail changes) after docetaxel monotherapy ranges from 6 % to as high as 67 %, with most studies reporting corticosteroid premedication [9]. The wide range of incidence was likely a result of various doses, schedules, and premedication regimens. Grade 3 skin toxicity (with corticosteroid premedication) reported with weekly docetaxel monotherapy (25–40 mg/m²/dose) ranges from 0 to 19 % [5, 9–14] whereas q3w docetaxel monotherapy (60–115 mg/m²/dose) ranges from 0 to 9.8 % [6–8, 12, 13]. Incidence of “severe” skin toxicity as high as 70 % has been reported in the literature, but mostly in early studies where corticosteroid premedication was not employed. In the product information label, the reported incidence of grade 3–4 cutaneous reactions (excluding nail changes) for docetaxel were 5 % for 100 mg/m² (breast cancer), 1 % for 75 mg/m² (lung cancer), and 0 % for 60 mg/m² (breast cancer) [14].

Docetaxel-induced skin toxicity has a variety of manifestations, including limb erythematous reactions, HFS, plaque-like erythrodysesthesia, erythema multiforme, nail changes, scleroderma, supravenuous discoloration, radiation recall dermatitis, desquamation, and flagellate erythema [15, 16]. HFS also known as palmar–plantar erythrodysesthesia (PPE) is a more severe skin reaction related to docetaxel as well as other cytotoxic chemotherapy agents. The syndrome includes a prodrome of dysesthesia, tingling sensation in the palms and soles, progressing to a bilateral, symmetric, burning pain with swelling and erythema that occasionally may extend beyond the palmar and plantar regions. Some patients may also present with desquamation with or without erythema [17, 18]. Childress and Lokich coined the term periarticular thenar erythema and onycholysis syndrome for docetaxel-induced HFS due to distinctive clinical presentations between docetaxel versus anthracycline/antimetabolite-induced HFS. However, more work is needed to confirm their conclusions that docetaxel-induced HFS should be designated as a separate syndrome [19]. Table 1 lists frequencies of skin toxicities and HFS seen in clinical trials in patients with [breast] cancer.

Currently, the etiology of docetaxel-induced skin toxicity is unclear. Some suggested a direct toxic effect of either docetaxel or polysorbate–80, the vehicle for docetaxel [20]. Others had hypothesized that PPE-related chemotherapeutic agents are excreted through the sweat glands which are abundant on the palms and soles [21, 22]. It was proposed that repeated and/or high doses of chemotherapeutic agents lead to cumulative toxic damage of the keratinocytes, which are particularly susceptible because of their rapid turnover rate. Probable risk factors include high density of sweat glands, absence of folliculosebaceous units, thick stratum corneum, and wide dermal papillae [23]. Bardia and colleagues reported a case series on five patients who experienced HFS following ddAC or taxane with pegfilgrastim. In all cases, the symptoms occurred 0–2 days after pegfilgrastim administration. The syndrome resolved or did not recur in four patients after pegfilgrastim was discontinued. The authors hypothesized that the pegylated filgrastim molecules enhances neutrophil infiltration in the basal layer and subsequently provoke inflammatory response in some patients [24]. A recent retrospective study reported that the use of H₂-blockers as premedication in breast cancer patients receiving docetaxel significantly

increased the risk of HFS (OR=2.55, $P<0.001$) and facial erythema (OR=3.00, $P<0.001$) that was attributed to a potential CYP 3A4-mediated drug–drug interaction between these agents and docetaxel [25]. Nonetheless, the study did not measure an effect of H₂-blockers on the AUC of docetaxel [26]. Dexamethasone is a moderate CYP3A4 inducer. It is conceivable that non-adherence to oral dexamethasone premedication might result in higher docetaxel serum concentrations. However, previous studies with docetaxel, several of which are included in the prescribing information, indicated that dexamethasone did not influence the clearance of docetaxel [14]. Additionally, it is important to note that docetaxel formulation was changed from a two-vial to one-vial system in 2010 (polysorbate-80 content/mg docetaxel is unchanged but has higher alcohol content/milligram). It is uncertain whether such change could account for increased risk of developing skin toxicities, although it is very unlikely.

Another conceivable explanation for the increased skin toxicity is the combination of ddAC preceding high-dose docetaxel use. To date, no existing prospective clinical trial has examined the efficacy and toxicity profile of ddAC q3w docetaxel regimen, and relatively few trials have looked at concurrent or sequential dose-dense doxorubicin and docetaxel [27–34]. Dose-dense doxorubicin monotherapy (75 mg/m²) followed by dose-dense docetaxel (100 mg/m²) resulted in a rate of grade 3 HFS of 42 % in one of the studies despite corticosteroid premedication [28]. A retrospective study revealed that 80 % of the patients who received ddAC (60/600 mg/m²) dose-dense docetaxel (100 mg/m²) regimen had grade 3 skin and nail toxicities and 50 % experienced grade 3 HFS [29]. A phase II study by Lambert-Falls and Modugno compared dose-dense docetaxel (100 mg/m²) followed by ddAC (60/600 mg/m²) versus 75 mg/m² followed by ddAC. Grade 3 HFS was observed in 25 % of the former patients, while only 11 % in the latter arm [32]. Antolin and colleagues recently reported the results of a phase II neoadjuvant study from patients who received dose-dense docetaxel (100 mg/m²) followed by ddAC (60/600 mg/m²). The incidence of grade 3 skin toxicity was reportedly 13.1 % during docetaxel [35]. A phase II study by Puhalla and colleagues demonstrated that the administration of docetaxel (75 mg/m²) after AC (60/600 mg/m²) in a dose-dense schedule resulted in higher incidence of HFS than the reverse sequence (29 vs 4 % grade 2/3 HFS, respectively) [33]. An interesting detail we noted from a phase II study reported by Cooper and colleagues that studied sequential dose-dense doxorubicin followed by q3w docetaxel (100 mg/m²) was that two of the first three patients of the study developed grade 3 HFS after the first dose of docetaxel and prompted protocol amendment to allow 3 weeks interval between the final dose of doxorubicin and first dose of docetaxel. The reported incidence of grade 3 HFS during docetaxel decreased to 2.8 % [31]. Collectively, these data and our experience reported here suggest that (1) dose-dense docetaxel at 75–100 mg/m² cause severe skin toxicity, therefore is not a feasible treatment option; (2) dose-dense docetaxel preceded by dose-dense doxorubicin and cyclophosphamide might increase the risk and/or severity of skin toxicity; and (3) it is imperative that the time interval between the final dose in ddAC and first dose of q3w docetaxel is at least 3 weeks apart.

At present, the most common approaches for the management of docetaxel-induced dermatologic toxicity are treatment interruption and dose reduction. A number of small studies and anecdotal reports have shown oral pyridoxine to be useful as a preventative and therapeutic agent [35, 36]. However, a recent randomized, double-blind, placebo-controlled study in 389 subjects failed to show the benefit of pyridoxine in preventing HFS associated with capecitabine therapy [37]. A phase II study by Scotte and colleagues evaluated the effectiveness of frozen glove therapy for the prevention of onycholysis over a 14-month period in 45 subjects, with prostate, non-small cell lung, and breast cancer [38]. Each patient wore patented frozen gloves (15 min before, during, and 15 min after infusion). The use of a frozen glove reduced nail toxicity from 51 to 11 % ($P=0.001$) and skin toxicity from 53 to

24 % ($P=0.001$). A follow-up study in 48 subjects with prostate, breast, or lung cancer who received docetaxel at 70–100 mg/m² over 1 h as mono- or combination therapy revealed a significant reduction in nail toxicity in the frozen sock-protected foot compared to the control foot (0 vs 21 %, $P=0.002$) [39]. However, no difference in the incidence of skin toxicity was noted (2 vs 6 %, $P=0.18$). Some have raised a concern about the potential of increasing the likelihood of cutaneous metastases of scalp cooling during chemotherapy due to decreased perfusion of the cooled skin [40]. Cooling of hands and feet is less extensively studied compared to scalp cooling. Long-term follow-up from the Dutch Scalp Cooling Registry will shed light on the safety of cutaneous cooling during chemotherapy [41]. Palliation of HFS symptoms has also been seen with the use of emollients/skin protectants. Adequate skin protection with the use of moisturizers/emollients, sunscreen, and friction minimization are common recommendations by health care professionals as prophylaxis for HFS. The use of topical dimethylsulfoxide [42] and oral vitamin E [43] as potential treatments for HFS were studied but data are limited. The use of corticosteroids (oral and topical) as treatments for chemotherapy-induced HFS yielded variable outcomes and remains controversial [44, 45].

Conclusion

Despite being well characterized in the literature, the etiology of docetaxel-induced dermatologic toxicity is unknown and evidence-based prevention and management strategies are lacking. General supportive care with occlusive emollients, pain management, and antibiotic use where appropriate appear to be useful. Our experience and some published reports suggest that docetaxel 75–100 mg/m² given subsequent to ddAC can lead to unacceptable rate of HFS. Our case series also serves as an example of how a drug shortage forces providers to use non-standard combinations or more toxic alternatives that may have detrimental effects.

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Fig. 1. Appearance of grade 3 HFS presented by case 1. **a** Presence of palmar erythema with profound desquamation and skin edema; **b** Papular and erythematous rash on the dorsal surface of the forearm. Presence of erythematous, desquamation is also apparent on the dorsal part of the hand

Table 1
Reported incidence of docetaxel-related skin toxicities/HFS from studies in breast cancer population

Study (year)	Stage	No.	Study phase	Treatment/regimen	HFS incidence, %		Skin Toxicities, %	
					All grades	Grade 3 0	All grades	Grade 3
Miller et al. (28)	II–III	40	II	I: A 75 mg/m ² q2w × 3, then Doc 100 mg/m ² q2w × 3 II: combination A-Doc (56/75 mg/m ²) q3w × 4	n/a	I: (A)0 (Doc) 42 ^a II: 0	n/a	n/a
Chan et al. (6)	IV	161	III	I: Doc 100 mg/m ² ; q3w	n/a	n/a	37.7	1.9
Schwartz et al. (29)	I–III	66	Other ^b	I: AC (60/600 mg/m ²) q3w × 4, then Doc 100 mg/m ² q3w × 4 II: AC (60/600 mg/m ²) q2w × 4, then Doc 100 mg/m ² q2w × 4	I: 5 ^c II: 70 ^c	I: 4 II: 50	I: 27 ^c II: 60 ^c	I: 4 II: 20
von Minckwitz et al. (30)	II–III	904	III	I: A-Doc (50/75 mg/m ²) q2w × 4 II: AC (60/600 mg/m ²) q3w × 4, then Doc 100 mg/m ² q3w × 4	n/a	n/a	n/a	I: 2.9 II: 7.1
Ford et al. (11)	III–IV ^d	42	II	Doc 35 mg/m ² q1w × 6 wk; 8wk cycle	n/a	n/a	46 ^e	19
Cooper et al. (31)	II–III ^f	39	II	A75 mg/m ² q2w × 3, 3 weeks interval ^g then Doc 100 mg/m ² q2w × 3	n/a	(A) 5.5 ^g (Doc) 2.8 ^g	n/a	n/a
Lambert-Falls and Modugno (32)	I–III	46	II	I: Doc 100 mg/m ² q2w × 4, then AC (60/600 mg/m ²) q2w × 4 II: Doc 75 mg/m ² q2w × 4, then AC (60/600 mg/m ²) q2w × 4	n/a	I: (Doc) 25 (AC) 0 II: (Doc) 11 (AC) 0	n/a	n/a
Puhalla et al. (33)	II–III	56	II	I: Doc 75 mg/m ² , q2w × 4, then AC (60/600 mg/m ²) q2w × 4 II: AC (60/600 mg/m ²) q2w × 4, then Doc 75 mg/m ² , q2w × 4	I ^h : 4 II ^h : 29	I: 4 II: 11	n/a	n/a
Rivera et al. (12)	IV	118	III	I: Doc 75–100 mg/m ² q3w ⁱ II: Doc 35–40 mg/m ² on D1,8,15 q4w ^j	n/a	n/a	n/a	j
Sparano et al. (3)	II–III	2,466	III	I: AC (60/600 mg/m ²) q3w × 4, then Doc 100 mg/m ² q3w × 4	I ^h : (AC) 0 (Doc) 3 I ^{hk} : (AC) <5 (Doc) <24.5	I: (AC) 0 (Doc) 2 I: (AC) <4.5 (Doc) <4		

Study (year)	Stage	No.	Study phase	Treatment/regimen	HFS incidence, %		Skin Toxicities, %	
					All grades	Grade 3	All grades	Grade 3
Stemmler et al. (13)	IV	102	II	II: AC (60/600 mg/m ²) q3w × 4, then Doc 35 mg/m ² q1w × 12	II ^h : (AC) <0.5 (Doc) 6	II: (AC) 0 (Doc) 3	II ^{h,k} : (AC) <6 (Doc) <38	II: (AC) <1.5 (Doc) <3
				I: Doc 75 mg/m ² q3w	n/a	n/a	I: 40.7 ^l	I: 5.6 [#]
Antolin et al. (34)	II–III	99	II	II: Doc 30 mg/m ² D1, D8, and D15 q4w			II: 29.2 ^l	II: 14.6 [#]
				Doc 100 mg/m ² q2w × 4, then AC (60/600 mg/m ²) q2w × 4	n/a	n/a	n/a	(Doc) 13.1 (AC) 0

A doxorubicin, Doc docetaxel, n/a not available

[#] P<0.05

^aAfter first docetaxel dose

^bRetrospective

^cGrades 2–3 reported only

^dUnresectable or metastatic

^eGrouped as “cutaneous,” inclusive of HFS

^fInoperable and large operable breast cancer

^gTwo of the first three patients developed grade 3 or 4 hand–foot syndrome after first dose of docetaxel prompted protocol amendment to allow 3 weeks interval between final dose of doxorubicin and first dose of docetaxel. The authors reported grade 3–4 HFS in 5/39 (12 % patients overall). Here, we excluded the first three patients before protocol amendment for our calculation

^hData for grades 2–4 available only in reference cited

ⁱStarting doses of docetaxel in the first cycle were 75 mg/m² (for q3w) or 35 mg/m² (q1w). If no grade 4 neutropenia lasting >7 days or associated with fever or infection, doses for second cycle were increased to 100 and 40 mg/m², respectively

^jNot listed among the reported grade3/4 toxicities

^kIncluding erythema, nail changes, pruritus, skin (other), pigmentation, urticaria, rash/desquamation, and dermatitis

^lSkin and nail disorders